REMARKS

Claims 1-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tuting & Albers in view of Roser and Volkin. For reason of solely expediting the prosecution, applicants have amended claim 1 to incorporate the limitation of now cancelled claim 2. Applicants believe that the amendment obviates some grounds of rejection raised by the Examiner. In view of the amendment made, and based on the foregoing argument presented, Applicants believe that the application is in condition for allowance. Reconsideration and re-examination are respectfully requested.

Formal Objections

Claims 2-20 have been objected because the Examiner thinks that Applicants failed to further limit the invention. Claims 3-20 have now been amended to address the Examiner's objection.

Claim Rejections – 35 USC 103

The Examiner acknowledges that a DNA pharmaceutical agent dosage form, having a dense core element coated with a **solid reservoir medium** containing the DNA pharmaceutical agent is not explicitly taught by Tuting & Albers. Further he states that DNA pharmaceutical agent dosage form further comprising a stabilizing agent that inhibits the degradative effects of free radicals, and the DNA pharmaceutical dosage form wherein the DNA pharmaceutical agent is supercoiled plasmid DNA is not taught by Tuting & Albers and Roser. However, the Examiner says

> *it would have been obvious to a person of ordinary skill ...to modify the DNA pharmaceutical agent dosage form having a dense core element...such that it is coated*

with a solid reservoir medium containing the DNA pharmaceutical agent as explicityly taught by Roser et al; and also such that it further comprises a stabilizing agent that inhibits the degradative effects of free radicals as explicitly taught by Volkin et al in order to preserve the supercoiled structure of the plasmid DNA to increase the ability to store the pharmaceutical DNA agent for longer period of time at 37°C...The person of ordinary sill in the art would have been motivated to make such modifications in the DNA pharmaceutical agent dosage form...

Applicants respectfully counter that Examiner is engaging in the impermissible hind-sight reconstruction.

At the time of filing there were already several methods for formulating plasmid DNA, and some that were specifically designed to stabilize plasmid DNA in its supercoiled form in liquid formulations and some within dry formulations. There was no suggestion, nor reason to believe, that improved stability could be achieved by combining two of the known stabilization techniques together.

Tuting & Albers is a general description of gene transfer using gold beads, and has little or no discussion of formulations or DNA plasmid stability. The formulations that are described on page 34 and 35 are formulations that are common in the art, and result in gold beads where DNA is precipitated onto the surface, in the presence of other materials, including spermidine and PVP. As Examiner concedes, there is no disclosure of DNA being present in a solid reservoir medium, nor any material that is intended to preserve the plasmid DNA in its supercoiled state by reducing the negative effects of free radicals. Tuting and Albers is, in effect, a generic description of DNA delivery using gold beads, and does not describe in any great detail the issue and problem of stabilization of the plasmid in its supercoiled form.

Roser is a description of solid dose pharmaceutical forms, in which the pharmaceutical, such as DNA, is stabilized within, for example, a polyol glass. There is no disclosure of a gold bead, or any dense core element, and no disclosure of plasmid DNA being stabilised in its supercoiled form. Roser is a disclosure, however, of DNA being held within the matrix of a glass polyol, and as such is in a dry form. Such formulations are not unique to Roser, see for example US5098893 (Frank). US5098893 in particular, column 5, lines 42-47, describes the dry glassy state of a formulation being sufficient to stabilize any material because the rate of chemical degradation of a substance is reduced in a glass to such a low level that the degradation effects are negligible over a normal shelf-life. US patent '893 (Frank) is attached herewith for Examiner's convenience.

Volkin, in complete contrast to Roser and Frank, describes how to make plasmid DNA stable when it is present in a liquid form. This is achieved by adding substances to the aqueous solution which either reduce the production of, or neutralise the effects of, free radicals - which are said in Volkin to be amongst the effector mechanisms of supercoiled plasmid degradation (page 2). The means to stabilise the DNA in liquid form are disclosed to be either free radical scavengers or metal ion chelators.

It is clear from Volkin and Roser that a number of different methods were available to a skilled person at the priority date to stabilize DNA, whilst only one of these authors mentioned the stabilization of plasmid DNA in its supercoiled form. Roser and Frank said that the reduced rate of degradative chemical reactions in a dry glass state would mean that the rate of degradation of DNA would be too slow to be relevant. Volkin on the other hand said that in a

liquid form (where chemical reactions occur at their unfettered speed) stabilization can occur if one reduces the pre-cursors of those degradative chemical reactions (the free radicals).

There is no suggestion in Volkin or Roser, that the Volkin's theory (of reduced free radicals) would have any effect in the dry, solid reservoir medium such as that disclosed in Roser or the present invention. The skilled person would simply not be motivated in any way to combine the teachings of Volkin and Roser, because they are not working towards the same mechanism of stabilization. Even if the skilled person were motivated to combine the teachings of the two documents, the skilled person might expect Volkin's suggestion to add a means to reduce the effect of free radicals to be completely superfluous and non-functional in a dry reservoir, such as a glassy polyol. The skilled person is taught in Roser and Frank that chemical reactions would not occur in a glass, and as such reducing the elements of that chemical reaction may have no benefit at all.

Quite unexpectedly, the present invention teaches that, in fact, combining the two theories of stabilization does indeed have a beneficial effect. Even in a solid reservoir medium, such as the glasses that are exemplified, adding agents that reduce the effects of free radicals can have a beneficial effect in stabilizing plasmid DNA in its supercoiled form. This is not taught nor suggested in Volkin or Roser, and the skilled man would have no motivation to combine these documents to arrive at the presently claimed invention. In concluding, Applicants respectfully re-emphasize that combining the three teachings into one without any teaching, suggestion or motivation would be an impermissible hindsight reconstruction.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit Account No. 19-2570, accordingly.

Respectfully submitted,

William T. Han
Attorney for Applicant
Registration No. 34,344

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-5263
Facsimile (610) 270-5090
N:han\apps\pgcases\pg4744\amendment